Dissertation On

THE INFLUENCE OF HELMINTHIASIS ON ALLERGIC ASTHMA

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CERTIFICATE

This is to certify that Dr. G. SHIV KUMAR, Post Graduate Student (March 2004 to February 2007) in the Department of Internal Medicine, Kilpauk Medical College, Chennai 600 010, has done this dissertation on "**THE INFLUENCE OF HELMINTHIASIS ON ALLERGIC ASTHMA "** under my guidance and supervision in partial fulfillment of the regulation laid down by THE TAMILNADU Dr M.G.R MEDICAL UNIVERSITY for the award of MD Degree in GENERAL MEDICINE .

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CONTENTS

AIM OF THE STUDY

1. **To study the influence of Helminthic Infection on the disease process of Allergic Asthma**

2. **To find out the prevalence of Helminthiasis in Atopic Asthma patients.**

INTRODUCTION

What represents a disease or infection in one scenario may well have a beneficial effect in quite another. There is growing interest at the international level on the possible interrelationship between helminthic infection and allergic asthma, although the exact nature of the relationship remains uncertain. Allergic asthma is one of the most common respiratory ailments in children as well as the adult population. Whereas most cases of asthma originate in childhood, the natural history of the disease is poorly understood.

In the developing tropical countries helminthiasis is a major public health problem. The epidemiologic observation that atopic asthma is very common and helminthiasis uncommon in developed countries and that the converse is true in developing countries has lead to the speculation that the two phenomena may be inversely related. However, the relationship between helminthiasis and allergic asthma remains largely uncertain.

It has been proven in various studies that despite equal living conditions, the intensity of parasite infection was greater among non-allergic individuals than allergic patients[30]. Chronic and persistent helminthic load can suppress the allergic responses by causing an IL-4 dependant activation of

non-specific polyclonal IgE production and thereby saturation of mast cells[29,2]. The allergen specific IgE gets diluted in this polyclonal IgE rise. This causes a fall in the atopic responses to specific allergens. It is also worthwhile to mention that as the socio economic status decreases the helminthiasis rate increases and serum IgE level rises[7,13].

In accordance with the above, parasite eradication can produce resurgence of allergic reactivity towards common environmental allergens in populations in whom this was suppressed by excessive polyclonal IgE[2].

The aim of this study is to find out the influence of helminthiasis on allergic asthma and thereby derive an insight into the disease process.

REVIEW OF LITERATURE

HISTORICAL BACKGROUND

Can parasites cure asthma?

This question has intrigued investigators for three decades, sometimes to the extent of self-testing. Turton [1978], out of curiosity infected himself with hookworms to test their beneficial effects. He observed a quick reduction in his asthmatic symptoms[3].

Though the relationship between helminthiasis and allergic asthma was enigmatic, the protective effect of worms was observed in early 70's. This idea flourished till the mid 80's but diminished after 1985 when a review on the subject concluded that the data "neither refute nor support the theory that parasite infection protects against asthma[16]".

However, there was a resurgence of the concept when investigators provided strong evidence for a protective effect. Lynch et.al suggested that lower socioeconomic status could confer protection against atopy due to increased incidence of childhood infections[7]. He also showed that regular anthelminthic treatment increased the skin reactivity to allergens in children[14].

Van den Bigelaar et.al. showed that schistosoma infection was associated with decreased skin reactivity to house dust mite in Gabonese children[33]. Cooper et.al demonstrated that parasite infestation protects against allergic sensitization and exercise induced wheeze[49].

Today the beneficial effects of worm infestation has come to be recognized by all in the wake of clear pathogenetic models and evidence based reports.

PATHOGENESIS OF ATOPIC ASTHMA

Atopic asthma frequently begins in childhood. Atopy is the genetic susceptibility to produce IgE antibodies directed towards common environmental allergens including house dust mite, animal proteins & fungi [Larsen 1992]. With the production of IgE antibodies, mast cells and probably other airway cells [T lymphocytes] are sensitized against specific allergens.

It has been proven by many studies that mast cells, activated T lymphocytes, Eosinophils, epithelial cells and macrophages are the key factors of the inflammatory process of asthma [Djukanovic et. al. 1990][11]. These

cells can cause the inflammatory response by various mediators, which might be pre – formed or newly synthesized in response to allergen exposure.

Of the newly synthesized mediators, the principle cytokine is IL-4. Reasons are:

- it is the critical early signal for B lymphocytes to switch over to IgE production.
- it produces increased VCAM expression and augments eosinophil recruitment.
- it is crucial for the development of TH2 regulatory response.[31]

Of the pre-formed mediators, neutral proteinases like Tryptase are essential for initiation of the inflammatory process. Broncho-alveolar lavage studies of allergic / non – allergic patients with or without asthma revealed that allergic asthma only had maximum concentration of tryptase after allergen challenge.[28] Other mediators of importance include histamine, prostaglandins, leukotrienes, TNF α and so on.

The inflammatory process begins with the interaction of the specific IgE [bound to mast cells] with a known allergen. This triggers mast cell destabilization and degranulation of preformed and newly synthesized mediators. The inflammatory process perpetuates rapidly with recruitment

and activation of other cells like eosinophils, neutrophils and lymphocytes. The use of cellular and molecular biologic techniques has lead to the revellation of sub-populations of CD4+ T lymphocytes [TH1 and TH2] which have been derived from uncommitted precursor TH0 cells. The differences between the two cell types are:

TH2 response	TH1 response
• Mediated through IL-4	• Mediated through IL-12, IFN–γ & TGF-β
• ↑ IgE synthesis	• Potentiates cellular immunity
• Eosinophil activation / ↑ VCAM expression	• No specific effect on osinophils[11].

The inflammatory process could be acute, subacute or chronic persistent [characterized by persistent cell damage and ongoing repair process]. The immunohistopathologic features include:

a. denudation of airway epithelium

b. collagen deposition beneath basement membrane

c. submuscosal edema / goblet cell hyper plasia

d. smooth muscle hypertrophy

e. inflammatory cell infiltration-Neutrophils, Eosinophils and Lymphocytes[11].

IMMUNE EFFECTS OF HELMINTHS

There are 2 dominant features of all helminthic infections:

- First, they are chronic and long lasting, affording slowly maturing parasites the time to reach target organs and reproduce.
- Second, they are the most efficient known inducers of TH2 immune response[31].

The interaction of parasite antigen with mast cell or eosinophil bound IgE triggers activation of TH2 response which produces IL-4, thus perpetuating the reaction. The IL-4 causes massive production of IgE by B lymphocytes which is a protective response. The markers of the response include elevated IL-4 production by polyclonally stimulated peripheral blood mononuclear cells (PBMCs), elevated serum IgE levels [normal <100 iu/ml; infected subjects 300 – 7000 iu/ml] and eosinophilia.

The association between helminths and allergic asthma was first explained by Lynch et.al[13]. It was observed by Shirakava et. al[35]. that the

rise in the incidence of allergies in Japanese children was associated with a reciprocal decrease in the cellular reactivity to mycobacteria. Also the disappearance of mycobacterial reactivity was closely paralleled by the loss of Ascaris infections. In another study done on children whose infections were cleared by anti-helminthic drugs patients developed heightened skin reactivity to house dust mite in contrast to untreated individuals[14].

The explanation for decrease in allergic tendency is that chronic and persistent helminthic infection produces a chronic antigen challenge and downregulation of immune process might be the immune system's natural response to continuous antigen exposure[31]. The two most important mediators of down regulation are IL-10 & TGF-β, because neutralising antibodies to these cytokines rescue reactivity[12,31].

CLINICAL FEATURES AND NATURAL HISTORY OF ALLERGIC ASTHMA

90% of childhood onset and 50% of adult onset asthmas are atopic in nature[1]. Atopy can manifest at any age, however it commonly occurs in childhood. Children commonly present with the triad of symptoms-cough, wheeze and breathlessness. The most common of these is breathlessness often associated with tightness of chest. These symptoms characteristically disturb the patient in the night or in the early hours of the morning.

Allergic asthma is an episodic illness with the patient experiencing symptom-free break periods. Seasonal variation is also a feature of allergy and points towards an allergen like pollen or spores which disseminate in that season. Allergic asthma attacks are usually accompanied by rhinitis and/or conjunctivitis. These are useful pointers for atopy because house dust mite, animal dander or pollen rarely ever cause asthmatic attacks without nasal manifestations.

The salient features of the course of asthma are its variability and unpredictability. The natural course is usually periods of normality punctated by exacerbations.

Allergic asthma beginning in childhood has a reasonable probability to remit at about adolescence[6]. In a study conducted in Finland, 108 asthmatic children were followed up for about 20-24 yrs. Among them one-fourth became symptom free; one-fourth experienced symptoms about once a week; one-half had airway hyper-responsiveness and only 18% had decreased FeV1 values. Risk factors for persistence of asthma include severe childhood asthma, beginning at an early age and association with atopic eczema.

Adult onset asthma remits less frequently, approximately 20% except when it occurs as a prolonged response to viral infection.

INVESTIGATIONS

- **SPIROMETRY**

Spirometry measurements [FeV1/FVC] has been recommended in NAEP – EPR-2 guidelines for diagnosis of asthma[32]. The test is instrumental in demonstrating reversibility of airway obstruction. The test is performed both prior to and after inhalation of a shortacting bronchodilator. Significant reversibility is indicated by an increase of $\geq$ 12% and 200 ml in FeV1 after inhaling bronchodilators [ATS. 1991]. The test is also helpful to assess the severity of the disease by comparison of the patients' results with reference

values based on age, height, sex & race. It is worthwhile to mention that the PEFR meters are better tools to monitor the course of the disease than to diagnose asthma.

- **BRONCHOPROVOCATION**

When and if spirometry tests are normal at presentation or produce inconclusive reports, the diagnosis can be made by demonstrating heightened airway responsiveness to histamine or methacholine. Investigative modalities for allergic asthma include

- **Routine blood examination:** Blood eosinophilia >6% provides supportive evidence for atopy.

- **Skin test reactivity:** Intradermal skin tests are of value in demonstrating atopy towards common allergens. The tests are done for common antigens like house dust mite, food particles like egg proteins, cockroach antigen etc[8].

The different grades of severity of the test are[48]:

Response measurement	Test assessment
i. Test same as control	Negative
ii. 2x control size / Flair <20 mm	1+
iii. 2x control size / Flair >20 mm	2+
iv. 3x control size / erythema	3+
v. wheal with pseudopods	4+

- **SERUM IgE:**

  Serum IgE measurements are contributory to the diagnosis of allergic asthma. Documented increase in specific IgE [for the inciting antigen] is confirmatory to the individual's sensitivity to that particular antigen. Ser IgE is also raised in helminthiasis, however it is an increase in total IgE [not specific] and is due to polyclonal activation by worms. Newer methodology for detecting total IgE rise is anti-IgE ELISA.

- **CHEST X-RAY** is mandatory to rule out other respiratory/cardiac illness.

- **HELMINTHIASIS**

The most important method for the diagnosis of ascariasis is by demonstrating eggs in feces [freshly passed]. In general, eggs are easily

visualized in a saline emulsion of feces. However in rare instances, when the infestation is light, eggs can be demonstrated only by concentration methods.

Other supportive evidence for harbouring intestinal worms include a peripheral blood eosinophilia and elevation of total IgE levels.

TREATMENT OF ALLERGIC ASTHMA

Goals of Treatment:

- To prevent chronic and troublesome symptoms [cough, breathlessness etc.,]
- Maintain [near] "normal" pulmonary function.
- Maintain normal activity levels [including exercise and other physical activity]
- Prevent recurrent exacerbations of asthma and minimize the need for emergency department visits or hospitalization.
- Provide optimal pharmacotherapy with minimal or no adverse effects
- Meet patients and family's expectations.

In general, a stepwise approach to gain control of asthma is preferred as per NAEP – EPR-2 guidelines[32]. The aggressive approach of gaining prompt control with a higher level of therapy is advocated. The sequential steps of management based on the severity of the disease are given below:

STEP	LONG TERM	QUICK RELIEF	EDUCATION
Step 4: Severe Persistent	**Daily:** • Inhaled steroid (high dose) • Long acting broncho dilator / sustained release long acting oral broncho dilators. • Oral steriods	Short acting inhaled bronchodilators	Individual Education and Councelling
Step 3: Moderate Persistent	**Daily:** • Inhaled steroids and / or • Long acting β_2 – agonist for night time symptoms/ sustained release theophylline or oral β_2 agonists.	Short acting β_2 – Agonist needed	Self monitoring Group education
Step 2: Mild Persistent	**Daily:** • Inhaled steroid (low dose) or Cromolyn / nedohromil may be tried • Zileuton / Zafirlukast for patients >12 yrs age	Short acting β_2 – Agonist needed	Self monitoring Group education
Step 1: Mild Intermittent	**No Daily medicines**	• Short acting β_2 – Agonist as & when required. • Use > time a wk may indicate the need for long term Control Rx.	• Teach basic facts of asthma • Inhaler / Spacer holding chamber techniques. • Control measures for allergens.

The management of allergic asthma involves a holistic approach to include all modalities of treatment available. The components include:

- patient education of the disease process and ways of control
- environmental modification/lifestyle
- pharmacotherapy
- immunotherapy-of doubtful value.
- rehabilitation and occupation.

PROGNOSIS:

The prognosis for allergic asthma is generally considered to be good especially for childhood onset disease with known allergen. The average percentage of children who continue to experience symptoms after 10 yrs of onset is approximately 41%. It is much less favourable for adult onset disease, however even when untreated, continuous progression from mild to severe asthma is unlikely unless confounded by other factors eg. Smoking[6].

MATERIALS AND METHODS

I. Setting:

A prospective study and analysis of patients aged 5 – 40 attending the allergy and asthma clinic at Govt. General Hospital, Govt. Royapettah Hospital & Institute of Child Health, Chennai.

II. Study Population:

The study was conducted over a six months period from June 2005 to Nov 2005. The study population largely belonged to the lower socioeconomic strata living in suburban Chennai. The patients, because of financial constraints had limited access to paid health services and were basically dependant on Govt. Health care setup. Fifty atopic asthma patients were chosen for the study and were followed up by outpatient department reviews.

III. Study Design:

Cohort study of 50 allergic asthma patients divided into 2 groups based on the presence or absence of the risk factor – helminthiasis.

IV. Inclusion Criteria:

1. Typical patients of atopic asthma as evidenced by
   - Clinical history – age of onset, seasonal variation, known allergen, family history
   - Physical examination – wheeze, associated allergic rhinitis, eczema
   - Investigation – skin test reactivity, spirometry

2. **Worm infestation** as proven by:
   - Investigation – Stool tests for eggs and one or both of the following criteria
   - Clinical history – Pruritis, Pica, Passing worms in stools
   - Supportive evidence – eosinophilia, serum IgE.

V. Exclusion Criteria:

- Comorbid conditions like pulmonary tuberculosis, cardiovascular illness and pregnant women were excluded.

- Patients who were smokers were excluded as it might confound the results.
- Occupations predisposing to lung diseases like cotton workers, cane factory & leather factory workers were excluded.

VI. **Patient Registration & follow – up** :

The information collected consisted of basic data including name, age, sex & occupation. The presenting complaints and a history of significant medical & surgical illnesses were noted.

Vital signs were recorded. The presence or absence of dyspnoea/ tachypnoea were noted. Manifestations of atopy like rhinitis/eczema were looked for.

Detailed systemic examination was done to observe features of severity of asthma like chestwall shape, accessory respiratory muscles involvement, wheeze etc. Patients were subjected to spirometry to confirm the diagnosis of asthma and also to ascertain the severity. An improvement of $\geq$ 12% in FeV1 / FVC was taken as reversibility. The

severity of the disease was assessed as per NAEP – EPR – 2 guidelines[32].

SEVERITY CLASSIFICATION[32]

Grade	Symptoms		PEFR (Variability) or FeV1
	Day	**Night**	
Mild Intermittent	≤ 2 days/wk	≤ 2 nights/month	≥ 80% [<20% variability]
Mild Persistent	> 2 days/wk	> 2 nights/month	≥ 80% [20-30 % variability]
Moderate Persistent	Daily	> 1 night/wk	>60% <80% [>30% variability]
Severe Persistent	Continual	Frequent	≤ 60% [>30% variability]

Intradermal skin tests with common allergens like house dust mite, black gram, green banana, sea foods etc, were done to document atopy. ELISA test for Ser IgE was done on a subset of population belonging to both the groups.

Stool tests with and without concentration techniques were performed on all subjects to detect eggs of helminth [ascaris]. Blood tests including total and differential counts were done to document absolute eosinophil count. A chest X-ray was done to exclude other respiratory /cardiac illness.

The patients were followed up in review outpatient clinics at 1 monthly intervals and the findings documented.

OBSERVATION AND ANALYSIS

In this prospective cohort study, the study population comprising of 50 patients of allergic asthma were distributed into two age-matched groups of 25 each, based on the presence or absence of worm infestation. The results of the observations were compared between the two groups at the end of the six month study period.

Group I → Worm Infested Asthma patients - 25

Group II → [Control] Non-Worm infested Asthma patients - 25

Total number of cases 50

Henceforth, in this chapter the two study groups will be mentioned as I & II only.

Groups	Cases
I	25
II	25

The software used for the analytical study was **NCSS [Number Crunch Statistical Software].** The statistical tests used to determine the significance of the results were '**Chi-Square Test and Two Sample T Test'.**

Agewise occurance:

Age group	Gp I	Gp II
<12 yrs	16 (64%)	12 (48%)
>12 yrs	9 (36%)	13 (52%)

In Group I, 64% of the cases belonged to the age group ≤ 12 yrs whereas in Group II 48% of cases were of the ≤ 12 yrs. The observation suggests that worm infestation involves more the pediatric population than adults. However the association was statistically insignificant ($p>0.05$).

The age group of the study population was between 5 yrs and 40 yrs.

Study group	Range	Mean	S.D.
Gp I	5 – 38	15.36 yrs	11.614
Gp II	5 – 40	18.16 yrs	13.368

The mean age of Group I patients was 15.36 yrs with a Standard Deviation of 11.614. The average age of Group II patients was 18.16 yrs with SD 13.368

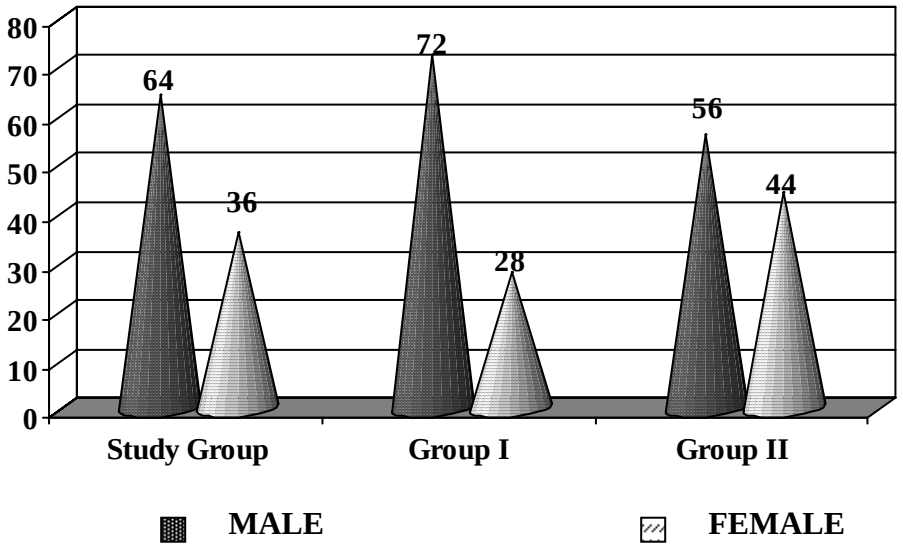
Sex Distribution:

Sex	Group I		Group II	
Male	No	%	No	%
	18	72	14	56
Female	7	28	11	44

There were 32 males, 18 females included in the study. Of the 32 males, 18 [56.25%] had worm infestation, whereas 14 [43.75%] did not. Of the 18 females, 7 [38.88%] were worm infested and 11 [61.12%] were not.

Male to Female ratio:

Total study group - 1.7 : 1



Group I - 2.5 : 1

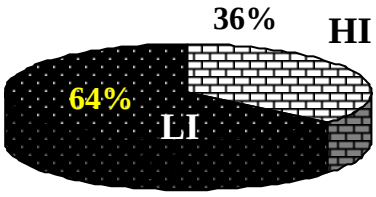
Group II - 1.2 : 1

In Group I the male to female ratio is much higher than in Group II suggesting worm infestation could occur more frequently in males than females.

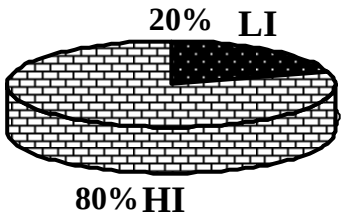
Socioeconomic status:

SE Status	Group I		Group II	
LI	No	%	No	%
	16	64	5	20
HI	9	36	20	80

The study population was divided into two socioeconomic strata as per the existing guidelines for population statistics.



Group I



Group II

	Monthly income
Lower Income Group	< Rs.1000/-
Higher Income Group	≥ Rs.1000/-

It is observed that in Group I 16 patients [64%] belonged to the lower income category and 9 patients [36%] were of higher income strata. This finding shows helminthiasis occurring with greater frequency in lower income group. In Group II, 5 patients [20%] were of lower income strata whereas 20 patients [80%] belonged to higher income category. Of the entire study population 42% were of the lower income group whereas 58% belonged to the higher income group.

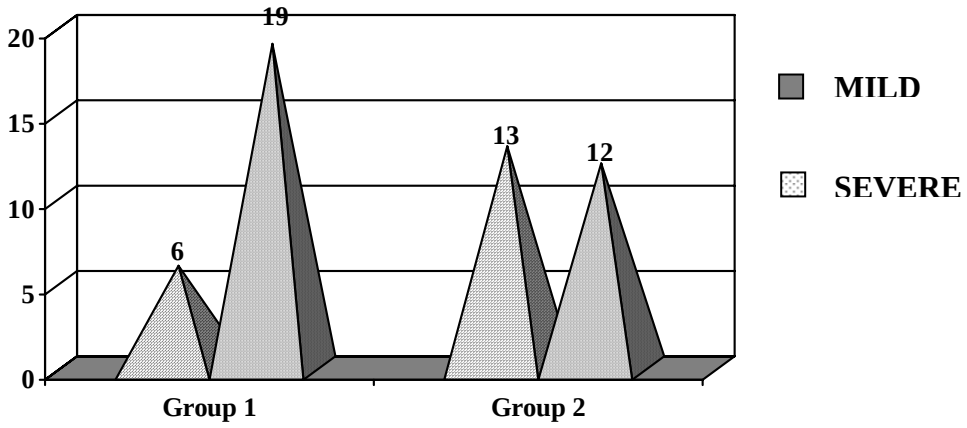
Asthma Severity & Clinical Course:

Group	**Severe**	**Mild**	**Total**	**'p'**
I	6	19	25	0.041399
II	13	12	25	
Total	19	31	50	

For analytical purposes, the severity of asthma was classified into two grades, by clubbing the existing NAEP classification.

Patients with Mild Intermittent and Mild Persistent asthma → Mild grade

Patients with Moderate Persistent and Severe Persistent asthma → Severe grade.



In Group I, 6 patients (24%) had severe asthma and 19 patients (76%) had a mild disease. In Group II, 13 patients (52%) had severe disease whereas 12 patients (48%) had a mild form of disease.

The Chi Square test was applied for this observation and the 'p' value obtained was 0.041399 [statistically significant if $p<0.05$]. As noted above the disease severity and the risk factor under consideration were having a statistically significant association.

Spirometry:

Groups	Range	Mean	SD	pvalue
I	60 – 99%	79.4 %	6.3179	0.04322
II	52 – 97 %	71.88 %	10.8448	

The spirometry readings of all the patients ranged from 52% - 99%. The mean spirometer reading for Group I patients was 79.4% $\pm$ 6.3179% and that for Group II was 71.88 $\pm$ 10.8448%.

To test the statistical significance the two sample T Test was applied, which gave a 'p' value of 0.04322 [Significant if $p<0.05$]. It is thereby observed that the association of spirometry with the presence of risk factor is statistically significant.

INVESTIGATIONS:

Absolute Eosinophil Count:

Groups	Mean	SD
I	404.24	140.0004
II	326.44	180.5727

The absolute eosinophil count varied between 116 to 732 /cumm. The mean AEC for Group I patients was 404.24 $\pm$ 140.0004. The mean for Group II was 326.44 $\pm$ 180.5727. The results on comparison were statistically insignificant.

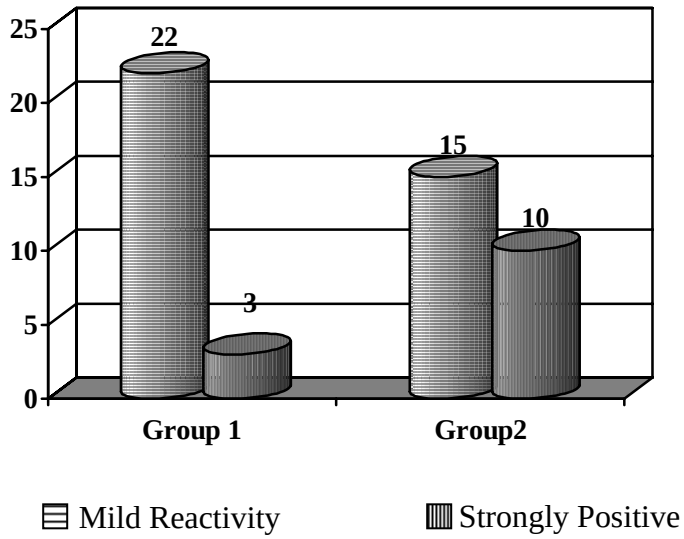
Skin Test Reactivity:

Groups	Just +ve	Strongly +ve	'p'
I	22	3	0.025
II	15	10	

Skin test reactivity was measured for every patient and graded as per standard criteria[8]. For purpose of analytical studies the reactivity was classified into two classes of increasing intensity.

Mild Reactivity - 1+

Strongly positive - >1+ [2+, 3+…]



The observation showed that in Group I, 22 patients [88%] had mild skin reactivity and 3 patients [12%] had strongly positive skin tests. In Group II, the distribution was 15 patients [60%] mild and 10 patients [40%] strongly positive. The statistical significance was 0.0254

Serum Immunoglobulin E:

Groups	Mean	SD
I	384.4	226.7527
II	338.0	180.4716

The serum total immunoglobulins were done for five patients in Group I and age matched 5 controls in Group II. The observation shows a mean serum IgE of 384.4 $\pm$ 226.7527 IU/ml in Group I and a mean of 338.00 $\pm$ 180.4716 IU/ml in Group II. The association was statistically insignificant.

Treatment:

Groups	Oral Steriods Yes		Oral Steriods No	
I	**No.**	**%**	**No.**	**%**
	2	8	23	92
II	7	28	18	72

The need for oral steroids were compared between the two groups and the results tabulated. In Group I, only 2 patients (8%) required oral steroids whereas 23 (92%) did not, during the entire study period. In Group II, 7 patients (28%) needed oral steroids for effective management and 18 patients (72%) did not. The association was statistically insignificant ($p>0.05$).

COMPARISON OF CLINICAL DATA:

Data Variable	**Group I**		**Group II**		**'p'**
1) Age					
• <12	16	64%	12	48%	
• >12	9	36%	13	52%	
2) Sex					
• M	18	72%	14	56%	
• F	7	28%	11	44%	
3) SE status					
• LI	16	64%	5	20%	
• HI	9	36%	20	80%	

4) Asthma Severity					
• Severe	6	24%	13	52%	0.041399
• Mild	19	76%	12	48%	
5) Spirometry	--	79.4%	--	71.88%	0.04322
6) Skin Test Reactivity					
• 1+	22	88%	15	60%	0.0254
• > 1+	3	12%	10	40%	
7) Oral Steriods	2	8%	7	28%	

On detailed analysis the following observations were made:

1) Among the children population who were studied 16 (57%) had helminthiasis. Compared with adults (40.9%) worm infestation was more prevalent in children. However the statistical significance was not appealing ($p>0.05$).

2) The study group comprised of 64% males & 36% females. The sex ratio for allergic asthma prevalence in children was 2.5 : 1 (male to female). In adult population the ratio was 1.1:1 (male : female).

3) The prevalence ratio of worm infestation among the male and female asthmatic population was 2.6:1 (M : F).

4) Of the total study group 42% were of the lower income strata. 76.19% of the patients in the lower income group had worm infestation, whereas only 31.03% of those in the average and high income groups had helminthiasis. It is thereby observed that worm infestation was more prevalent among lower income group.

5) Among the study population, 38% (19 pts) had a severe course. Of the patients with severe disease, 31.57% (6 pts) were of Group I and 68.5% (13 pts) were from the Group II. Ratio of non-worm infested to worm infested patients with severe course 2.2 : 1.

6) It is a worthwhile observation that among the lower income group only 19.04% had severe disease, whereas among the higher income group 51.72% experienced a severe course.

7) The skin test reactivity was of mild grade (1+) in 74% of the study group. In this grade 59.45% (22 pts) were of Group I. In the strongly reacting grade only 23% were from Group I, whereas 76.92% were from Group II.

8) During the study only 9 patients (18%) needed the institution of oral steroids for asthma management and of these 77.78% were of Group II.

9) The number of hospital admissions for severe disease was17 admissions over the 6 month study period. Among the admissions 41.17% were of Group I and 58.84% were from Group II.

10) It is noteworthy that despite mean IgE in Group I (384.4 IU/ml) being higher than the mean (338.0 IU/ml) in Group II, the skin reactivity was lower than Group II. (12% Vs 40%).

PREVALENCE OF WORM INFESTATION IN ALLERGIC ASTHMA PATIENTS:

Total patients screened - 108

Prevalence of positive stool tests – 25

Prevalence rate - 23.15%

Distribution of ascariasis:

	< 12 yrs	**> 12 yrs**	**Total**
Male	12	6	18
Female	4	3	7
Total	16	9	25

Prevalence in male to female ratio **2.6 : 1**

Prevalence in child to adult ratio **1.8 : 1**

Outcome:

Groups	Worsened	Improved	'p'
I	6	19	0.041399
II	13	12	

During the course of the study 24% of Group I patients worsened with frequent exacerbations, emergency visits, hospital admissions and poor Pulmonary Function Test performance. In Group II 52% of patients had a worse course. In both the groups 76% and 48% of patients had a steady improvement in their clinical status.

The outcome was tested for statistical significance by means of Chi-Square Test and the p value obtained was 0.041399 (significant).

DISCUSSION

The Hygiene Hypothesis:

Over the past 3 decades the incidence of allergic asthma has increased substantially in the developed countries. The most probable explanation is that the improved hygiene condition has lead to decreased incidence of childhood infections which in turn predisposed to increased expression of allergic diseases – Hygiene Hypothesis[23,36,37]. This is supported by the observation that in children belonging to the lower socioeconomic status and large households, multiple and repeated intestinal helminthic infestation protects against allergic diseases[36,37].

A concise model of the influence of helminthiasis on allergic asthma was given by Lynch er.al[13]. who have done pioneering work in this field. With mild worm infestation, there is an increase in the allergic reactivity due to non – specific potentiation of polyclonal IgE antibodies against parasite antigens. However, this increase reaches a peak beyond which chronic and persistent worm load and antigen challenge suppresses the allergic reactivity to specific allergens[25].

Cooper et.al showed that active infection with geohelminth parasites [as proven by increased IgE and anti-ascaris IgG4] exerted a protective effect against allergic asthma in school age children living in endemic regions[35]. He demonstrated a negative association between high levels of IgE and skin test reactivity.

Supportive evidence for this aspect was produced by Lynch et.al. when they proved increase in the prevalence of allergy after long term anthelminthic treatment of worm infested children[14]. Furthermore, results of intervention studies in Venezuela demonstrated that monthly anthelminthic treatment of children for 18 months, resulted in an increase in the prevalence of allergy[48].

Our study was designed to explore the interrelationship between worm infestation and allergic asthma in the population of patients attending the asthma clinic at Govt. Royapettah Hospital, Govt. General Hospital and Institute of Child Health, Chennai.

PREVALENCE OF ASCARIASIS IN ALLERGIC POPULATION

There have been very few global studies to ascertain the prevalence of ascaris infection. However an estimated one billion infected persons worldwide was proposed by Kazura [2000]. At this rate, ascariasis is the most common human helminthic infection[47].

Many regional studies were conducted to find out the prevalence of ascariasis in allergic individuals of various socioeconomic strata. Lynch et.al. showed that there was an inverse relationship between socioeconomic level and helminthic prevalence. In the lower socioeconomic level the prevalence was 47.6%[7]. In another study, the prevalence of light to moderate ascariasis in atopic population was estimated to be 40%[22].

Comparative studies of ascaris prevalence between allergic and non-allergic persons have yielded conflicting results. Kayhan .B et.al. found that the ascaris infection rate among atopic asthma patients was much more than among non –atopic controls [40% Vs 14%][4].

In contrast with the above, Cooper et.al. observed an increase in the prevalence of ascariasis [81.6%] in non-atopic children as compared with atopic [18.4%][45]. Lynch et.al. also supported this view by the observation of reduced worm burden in atopic patients[25].

The explanation for reduced prevalence of ascariasis in allergic asthma patients was given by Peisong et.al. A common asthma associated genetic variant of the transactivating factor for TH2 immune signalling – STAT-6 [Signal transducer and transactivating factor – 6] [46] had a very significant relation with increased resistance to ascaris infection. The other probable explanations for the inverse association between worm infestation and allergic asthma are elaborated in the section of Pathogenesis.

In our study the prevalence of ascariasis in allergic asthma patients was found to be 23.15%. However, the prevalence among non-atopic persons was not available for comparison, as this was not the primary aim of the study.

PATHOGENESIS

Why and how is allergic asthma moderated by worm infestation?

The answer to this question lies in the fact that there are striking similarities between immune response to helminthes and allergic response to allergens. In particular, both are characterized by:

- Enhanced TH2 responses with high levels of IL-4, IL-5 and IL-13
- High levels of IgE production
- Eosinophilia[31]

Woolcock et.al showed that many individuals remain free of clinical manifestations of allergic disease despite possessing all the above mentioned elements thought necessary to precipitate disease[21]. Helminthes are the most powerful known inducers of IgE production and are associated with very high total IgE levels.

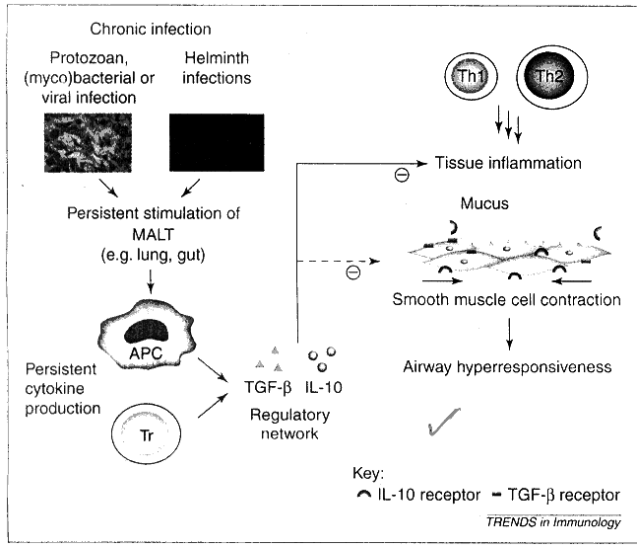
There are two plausible pathogenetic models which have so far explained the protective effects of helminthic infection on allergic airway disease.

Model 1:

Hagel, Lynch and coworkers proposed that the high levels of total IgE due to worm infection saturated the FCεR1 receptors on mast cells. Hence the allergen specific IgE which is diluted in this effect finds very few FCεR1 receptors to engage[14,48]. Supportive evidence for this hypothesis was given by Lynch et.al, who showed that anthelminthic treatment of children was followed by increased skin reactivity paralled by reduced total IgE levels[14].

Model 2:

Holt PG et.al suggested that persistent stimulation of mucosal immunity in organs such as the gut, 'educated' the immune system to react to allergies with



(adopted from TRENDS in IMMUNOLOGY)[31]

a beneficical immune profile. This favourable response is achieved by down – regulation of inflammatory process by the anti-inflammatory network of IL-10 and TGF – β[58].

Maria et.al[31]. supported this model and proposed that anti-inflammatory effects of IL-10 and TGF – β are the key factors for lower prevalence of allergic diseases in such populations. Also by multiple logistic regression analysis it was proven that of all the immunological parameters, parasite induced IL-10 significantly reduced [by 53%] the skin reactivity to house dust mite[33].

CLINICAL FEATURES

There are innumerable factors which moderate the expression of allergic asthma. Increased levels of exposure to allergens, air pollution, exposure to animals, diet, to mention a few can alter the presentation as well as the course of asthma. Of particular interest are infectious diseases like measles, Hepatitis A and parasite infections which have been associated with protection from atopy[36].

Chronic geohelminthic infections are known to have anti-inflammatory effects which suppress allergic airway disease[51]. This relationship has been

more consistently observed in the developing countries than the affluent nations[34,50]. Cooper P.J. et.al showed strong protective effects of helminthiasis against allergic asthma[45].

As regards the symptoms of allergic asthma, increased worm burden has been observed to significantly reduce the airway inflammatory signs[49]. The most beneficial influence has been found on exercise-induced wheeze. Also a rested case control study in Ethiopia showed significant protective effects of ascariasis against recent wheeze[51].

However there have also been conflicting reports of paradoxical increase in asthma prevalence in ascaris infected population in East Germany and China[15,29]. How can worms be both protective and detrimental to allergic asthma? The answer to this question is in 2 divisions:

- The intensity of worm infection and transmission is the most important determinant of its influence on allergic asthma. When the worm burden / transmission is low in the community [eg. Urban groups of high socioeconomic strata] this allergic reactivity is high.

Conversely in regions where the worms are endemic and transmission rate is high, the reactivity is low[13].

- The timing of helminthic infection is the second major determinant. In highly endemic regions, infections occurring quite early in childhood are associated with lowest rates of allergic asthma[52,49].

In our study worm infested asthmatics were compared with non-worm infested controls and the disease severity assessed as per NAEP – EPR – 2 guidelines in each group over a 6 month period. 24% of the worm-infested group had severe disease as against 52% in the non-worm group. The relationship was statistically significant (p=0.041399).

INVESTIGATION

Spirometry:

Damtew et.al compared the disease severity between 2 populations of allergic asthma patients [worm group and non-worm group] and inferred that ascaris infection had a specific protective effect against wheeze and improved spirometry record [p=0.01] [54].

Lynch et.al. provided support for this observation by instituting anthelminthic treatment to a population of slum children where ascariasis was hyperendemic. He observed that there was a significant reduction in the pulmonary performance of the treated group and increase in the skin reactivity[17].

In our study, spirometry was done for all the patients at diagnosis and once during follow up. The mean reading in the worm group was 79.4 $\pm$ 6.3179% and that in the non-worm group was 71.88 $\pm$ 10.8448%. The difference was statistically significant [p=0.04322], showing a beneficial effect with ascariasis.

Serum IgE:

Cooper et.al. provided evidence for the strong protective effect of worm induced high IgE levels against skin test reactivity to allergens [p=0.02]. This negative association could be explained by mast cell saturation theory[45].

Lynch et.al. observed that as the parasite prevalence increased, the serum IgE levels also increased paralleled by a fall in skin reactivity to allergens[7].

In our study serum total IgE was done in a subset of population representative of the two groups. The mean IgE in the worm group was 384.4 $\pm$ 226.7527 IU/ml and that in group II was 338.0 $\pm$ 180.4716 IU/ml. The difference was statistically insignificant ($p>0.05$).

Skin test reactivity:

Lynch et.al. observed a significant decrease in the skin reactivity to allergen challenge with increasing worm burden among patients in the lower socio-economic strata[7]. Another study conducted on school children in Ecuador showed decreased intensity of skin test reactivity with increased worm burden[49].

In our study skin test reactivity was performed for all patients and the results documented. In Group I 88% of patients had mild reactivity whereas 12% had strongly positive results. In comparison, 60% of Group II patients had mild reactivity and 40% had strongly positive results. The statistical significance of the difference was $p=0.0254$

TREATMENT:

The patients were treated for allergic asthma as per the existing guidelines according to disease severity[32]. Since our study was not contemplated to be interventional, anthelminthic treatment was not given. However, the patients were informed about their worm status. Only those patients who refrained from anthelminthic treatment were included in the study group upon consent. At the end of the study period, deworming agents were given to Group I patients under careful observation.

OUTCOME

In our study the influence of worm infestation on allergic asthma was sought. Similar to other studies mentioned above, asthma occurred with greater severity in patients without helminthiasis and hence the inference was that worm infestation had a protective effect on allergic asthma.

UNANSWERED QUESTIONS:

Having arrived at the inference of the study, there are still a few unanswered querries which remain to be explored:

- Increasing urbanization globally has lead to decrease in geohelminth infections which in turn has lead to increase in asthma prevalence. Could urbanization be attributed to this rise?

- Can strategies like early desensitisation or antigen overload of parasite antigens prevent the expression of allergic asthma later in life?

- Given that eradication of parasites is a universal public health goal, are we failing to understand any potential adverse effect by disturbing nature's fine balance?

Allergic asthma is a complex interaction of the human immune apparatus with the environment. Parasite exposure is but one of the environmental factors which have a bearing on the expression of the disease. There are innumerable other factors like Hepatitis A infection, maternal smoking, childhood respiratory infections to mention a few. Hence, it is recommended that large multicentric trials be taken up to study the influence of parasite infection along with other confounding agents on allergic asthma.

FUTURE TRENDS:

The future in allergic asthma is the use of parasite antigens as immunomodulatory agents. Imai and Fujita[59] have identified an IgE inducing factor DiAG (Dirofilaria immitis derived antigen) purified from filarial parasites. Inoculation of this antigen has proved successful in suppressing allergy and Type 1 DM in animal models. The day is not far when such interventions are human tested, opening up a new portal towards understanding and managing allergic asthma.

SUMMARY AND CONCLUSION:

Fifty patients of allergic asthma were divided into two study groups based on the presence or absence of worm infestation. They were followed up for a period of six months, clinical course and investigations compared.

- → The prevalence of ascariasis in allergic asthma patients was 23.15%.
- → There was no statistical significant difference in the age wise worm infestation rates.
- → The prevalence ratio of helminthiasis among male and female asthmatic population was 2.6 : 1.
- → The study also points out the significant difference in worm infestation rates between lower and higher income group (1.7:1).
- → Helminthiasis was associated significantly with milder disease course than the control group (p=0.041399).
- → The presence of worm infestation was significantly associated with improved performance of spirometry (p=0.04322).
- → The skin test reactivity was significantly reduced in the worm group as compared to the non- worm group (p=0.0254).
- → There was no significant difference in the IgE levels between the two groups.

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PROFORMA

(Modified from ISAAC questionnaire)

Date:

Name : Age/Sex: Occupation:

Residence: Educational Status Volunteer No.

Income : LI : ☐ HI : ☐

Specific History:

1. History s/o. Atopy : skin involvement/rhinitis/conjunctivitis/seasonal variation

2. History of Asthma (cough/wheeze/ chest tightness) : episodic/night awakenings/relief with bronchodilators

3. Physician diagnosed Asthma: Y / N

4. Onset of Asthma :

5. Duration of illness : Months / Years

6. Severity of symptoms : ☐ Days /Wk ☐ Nights/Months

   Loss of school/workdays / per month

7. Present Treatment :

8. History s/o. Helminthiasis

a. Passing worms in stools/mouth : Y / N

b. Pica / Perianal Pruritis : Y / N

Past History:

a. Severity: ☐ Days / Week ☐ Nocturnal symptoms / month

c. Other diseases

Personal History: Smoker – Active / Passive Tobacco / Cigar / Beedi

Family History : Atopy / Asthma Y / N

Treatment History:

a. Hospitalisation for Asthma : / Year / Month

b. Emergency Department Visits : / Year / Month

c. Treatment given for Helminthiasis : Y / N

d. Any other illness :

Occupation History: **a. Type**

b. Correlation with Symptoms

CLINICAL EXAM:

a. Vital Parameters : Pulse BP RR

b. General Examination : Dyspnoea (Y/N) Fever (Y/N) Pallor (Y/N)

Ht. Cms. Wt. Kgs.

Skin Eyes

ENT

c. Systemic Examination:

i. RS: Wheeze / Y/N **Spirometry :**

ii. CVS : Before bronchodilator %

After bronchodilator %

iii. Other systems :

Investigations:

a. Hb%

TC

DC

b. AEC

c. CXR – PA View :

d. Stool – Ova /eggs:

e. Skin test reactivity:

f. Serum Total IgE :

MASTER CHART

Sno	Age/ Sex	Income Group	Spirom etry	Absolute Eosinophil Count	Stool Test for Eggs/ova	Serum IgE IU/ml	Skin Test [Intradermal]	Need for Oral Steriod	Hosp. Admn.	Emer. Visits	Severity	Outcome
1	9/M	LI	80/93%	196	+	572	2+	NO	1	1	MP	Improved
2	20/M	HI	75/90%	468	+	420	2+	NO	-	1	MoP	Worsened
3	34/F	LI	86/98%	516	++	50	1+	NO	-	-	MI	Improved
4	11/F	HI	62/78%	348	+	600	1+	YES	-	6	MoP	Worsened
5	27/M	HI	82/96%	532	+	-	1+	NO	-	-	MI	Improved
6	9/M	LI	81/93%	364	+	-	1+	NO	-	-	MI	Improved
7	39/M	LI	77/91%	384	+	-	1+	NO	1	1	MoP	Worsened
8	9/M	LI	82/97%	496	+	-	1+	NO	-	-	MI	Improved
9	9/M	LI	80/96%	640	+	-	1+	NO	-	-	MI	Improved
10	5/M	HI	84/96%	432	++	-	1+	NO	-	-	MI	Improved
11	5/M	HI	84/97%	340	+	-	1+	NO	-	-	MI	Improved
12	27/M	LI	83/96%	544	++	-	1+	NO	-	-	MI	Improved
13	7/M	LI	80/96%	352	+	-	1+	NO	-	-	MI	Improved
14	11/F	LI	84/98%	624	+	-	1+	NO	1	1	MI	Improved
15	29/F	HI	60/72%	216	+	280	2+	YES	1	4	SP	Worsened
16	8/M	LI	82/95%	434	+	-	1+	NO	1	-	MI	Improved
17	6/M	LI	80/94%	384	+	-	1+	NO	1	-	MP	Improved
18	5/M	HI	82/95%	348	+	-	1+	NO	-	1	MI	Improved

Sno	Age/ Sex	Income Group	Spirometry	Absolute Eosinophil count	Stool Test for Eggs/ova	Serum IgE IU/ml	Skin Test [Intradermal]	Need for Oral Steriod	Hosp. Admn.	Emer. Visits	Severity	Outcome
19	6/F	HI	81/95%	300	+	-	1+	NO	-	1	MP	Improved
20	6/M	HI	82/98%	260	++	-	1+	NO	-	1	MI	Improved
21	5/M	LI	81/95%	288	+	-	1+	NO	-	-	MI	Improved
22	18/M	HI	82/96%	540	+	-	1+	NO	-	-	MI	Improved
23	38/F	LI	82/99%	132	+	-	1+	NO	-	1	MP	Improved
24	9/F	LI	66/80%	312	+	-	1+	NO	1	2	MoP	Worsened
25	32/M	LI	71/92%	656	+	-	1+	NO	-	2	MoP	Worsened
26	10/M	HI	58/72%	732	-	572	2+	YES	1	4	SP	Worsened
27	39/M	HI	70/85%	184	-	180	2+	NO	-	2	MoP	Worsened
28	30/F	HI	65/78%	192	-	-	1+	NO	-	2	MoP	Worsened
29	13/M	HI	76/89%	460	-	-	2+	NO	-	2	MoP	Worsened
30	36/M	HI	80/96%	256	-	-	1+	NO	-	-	MI	Improved
31	12/F	LI	80/94%	256	-	-	1+	NO	-	-	MI	Improved
32	18/F	HI	82/97%	186	-	-	1+	NO	-	-	MP	Improved
33	5/M	LI	81/94%	485	-	-	1+	NO	-	1	MI	Improved
34	38/F	HI	56/74%	216	-	-	2+	YES	1	3	SP	Worsened

Sno	Age/Sex	Income Group	Spirometry	Absolute Eosinophil count	Stool Test for Eggs/ova	Serum IgE IU/ml	Skin Test [Intradermal]	Need for Oral Steriod	Hosp. Admn.	Emer. Visits	Severity	Outcome
35	17/M	HI	83/96%	324	-	-	1+	NO	-	-	MI	Improved
36	14/M	HI	56/70%	312	-	250	2+	YES	1	6	SP	Worsened
37	5/M	HI	55/74%	336	-	-	1+	YES	2	4	SP	Worsened
38	30/M	HI	81/95%	736	-	450	1+	NO	-	-	MP	Improved
39	6/F	HI	82/95%	168	-	-	1+	NO	-	1	MP	Improved
40	5/M	HI	82/96%	360	-	-	1+	NO	-	-	MI	Improved
41	5/F	HI	75/90%	124	-	-	2+	NO	1	3	MoP	Worsened
42	5/F	HI	66/86%	520	-	210	3+	NO	1	1	MoP	Worsened
43	20/M	HI	52/70%	380	-	-	2+	YES	-	4	SP	Worsened
44	40/F	HI	58/72%	124	-	-	3+	YES	-	4	SP	Worsened
45	6/M	LI	81/93%	116	-	-	1+	NO	1	-	MI	Improved
46	12/M	HI	71/90%	368	-	-	1+	NO	1	3	MoP	Worsened
47	40/F	LI	59/73%	288	-	-	2+	YES	-	6	SP	Worsened
48	35/F	HI	80/96%	204	-	-	1+	NO	-	1	MP	Improved
49	7/M	LI	83/95%	192	-	-	1+	NO	-	4	MP	Improved
50	6/M	HI	81/97%	640	-	-	1+	NO	1	1	MI	Improved

ABBREVIATIONS: MI – Mild Intermittent, MP- Mild Persistent, MoP - Moderate Persistent, SP – Severe Persistent

ABBREVIATION

IL -4	Interleukin 4
IgE	Immunoglobulin E
VCAM	Vascular Cell Adhesion Molecule
TH1	T Helper 1
TH2	T Helper 2
TNF-α	Tumor Necrosis Factor α
TGF-β	Transforming Growth Factor β
IFN–γ	Interferron γ
FeV1	Forced Expiratory Volume 1
FVC	Forced Vital Capacity
NAEP- EPR2	National Asthma Education Programme – Expert Panel Report 2
ATS	American Thoracic Society
PEFR	Peak Expiratory Flow Rate

ELISA	Enzyme Linked Immunosorbent Assay
NCSS	Number Crunch Statistical Software
LI	Low Income
HI	Higher Income
AEC	Absolute Eosinophil Count
IgG4	Immunoglobulin 4
STAT-6	Signal Transducer and Transactivating Factor -6
IL-10	Interleukin 10
DiAG	Dirofilaria Immitis Derived Antigen
ISAAC	International Study On Asthma And Allergies in Children